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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,609	12/28/2000	David Robertson	1242/27/2/2	6747

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,609	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on June 30, 2004 has been entered and considered.

2. The instant application filed on December 28, 2000 claims benefit of US provisional applications 60/173,682 filed on 12/29/1999 and 60/175, 456 filed on 1/11/2000.

3. Claims 1-17 are pending.

Response to arguments

4. Applicants' arguments are fully considered and found persuasive in part.

5. With regard to the objection to the specification, made in the previous office action, Applicants' amendment and arguments are fully considered and the objection is withdrawn herein in view of amendment.

6. The following is the rejection made under 35 USC 112, first paragraph (enablement):

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in orthostatic intolerance, does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal NE transport in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the invention:

The claims are drawn to a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject. The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Breadth of the claims:

Claim 1, is drawn to a method of screening for susceptibility to sub-optimal norepinephirne (NE) transport in a subject. Claim 2 is further limiting the claim 1 to orthostatic intolerance and claims 3, 6-7, 9-13, and 16-17 are drawn to the said method of claim 1, further limiting the method. Claims 4-5, 8, 14 are drawn to a method of screening for susceptibility to sub-optimal norepinephirne (NE) transport in a subject with a detection of polymorphism in NE transporter gene transmembrane domain of exon 9 comprising G to C transversion resulting a in a NE transporter encoding polypeptide having a proline at position 457.

Amount of Direction and Guidance

The specification discloses the identity of a specific C to G nucleotide change which result in an alanine to proline change in amino acid position 457 (A457P) in a proband having orthostatic intolerance (Fig. 2A-2B). The specification on page 9, asserts a comparison of this mutation to a wild type NE transporter (NET) correlation among the related murine and bovine and frog NET

with that of human and further asserts the presence of this mutation in the proband having orthostatic intoleranace and in the family members of the proband (Fig. 2C-2F). The specification teaches that the mutation (A457P) is correlated to NE transport and its presence in the orthostatic intolerance. The specification also discloses the identification of the position of the mutation to the G to C transversion at base 237 within exon 9.

Presence and Absence of working examples:

The specification discloses a method of identifying exon 9 mutation, that is A457P in a proband (having orthostatic intolerance), with allele specific oligonucleotides (SEQ ID Nos. 9 and 10). The specification also provides primer sets for amplification of other exons of human NET gene. The specification also provides a silent (c154a) and missense (g237c) mutations in exon 9, proband being heterozygous for both of theses mutations, wherein the missense mutation is correlated with coding alteration of alanine to proline (A457P) within a highly conserved region of transmembrane domain of exon 9 (Example 4). The examples 5-6 in the specification establish a positive correlation between the presence of the mutant allele (AP) and the abnormal clearance of NE in orthostatic intolerance. Although the specification asserts identification of additional single nucleotide polymorphisms in human NET gene, the specification does not demonstrate any correlation between the NE transport in general with any specific mutation except for the correlation of the mutation A457P in orthostatic intolerance. Thus the specific mutation was correlated with the NE transport in orthostatic intolerance and not with the general NE transport in a subject.

Level of Predictability and unpredictability in the art :

Predictability in the art suggests mutations in other exons of the NET gene, however no specific mutation is associated with any specific type of norepinephrine transport or a disease, for example Stober et al. (Amer. J. Med. Genet., Vol. 67, pp. 523-532, 1996) teaches 13 DNA variants of NET gene, none of which is associated with any major psychiatric diseases. However, the art does not establish a predictable association that any specific mutation in NET is predictably associated with the broadly recited "sub-optimal NE transport" system. The art is further silent with regard to a predictable association between any specific mutation in NET and NE transport in general. The claims further broadly encompass screening for susceptibility to sub-optimal NE transport by detecting a polymorphism in NET gene. The specification, however does not establish a statistically significant association with any of the disclosed mutations in NET gene, with the susceptibility to sub-optimal NE transport (except for the A457P mutation in exon 9 in orthostatic intolerance), that would establish all mutations or polymorphisms result in the susceptibility to sub-optimal NE transport. Further, to date, no teaching is available in the art with regards to a universal correlation between any mutation in NET gene and an association with any general or specific susceptibility to NE transport. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with the susceptibility to sub-optimal NE transport. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of a polymorphisim in NET gene with general susceptibility to sub-optimal NE transport. In addition, the specification does not establish the identity of all specific critical nucleotide or amino acid alteration(s) in NET gene that are associated with the susceptibility to the sub-optimal NE transport. Since the specification has not identified any

polymorphism would result in susceptibility to sub-optimal NE transport, it is further unclear whether these mutations or any specific mutation will have a significant affect or not.

Level of Skill in the Art:

The level of skill in the art is deemed to be high.

Quantity of Experimentation Necessary:

It would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that any mutation in NET gene is significantly associated with susceptibility to NE transport. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different polymorphims, to determine if any general alteration or mutation in NET gene, was associated with general susceptibility to sub-optimal NE transport. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art.

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the presence of a working example which does not address the scope of the claim and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to arguments:

With regard to the above rejection, Applicants' arguments and amendment are fully considered and found not persuasive. Applicants' argue that specification broadly enables a method for screening for sub-optimal NE transport in a subject and points out that the specification enables a method in subjects with OI (orthostatic intolerance) is not limited to subjects with OI, can be equally applicable to subjects suspected of suffering from sub-optimal NE transport. Applicants' arguments are fully considered and found not persuasive because the specification enables a method of screening a subject with OI for sub-optimal NE transport, wherein the method clearly associates a specific mutation (A457P) with a subject with OI and does not provide that any polymorphism in NE transport gene in general, is associated with sub-optimal NE transport. In addition, the disclosure does not provide any enablement that the specific mutation (A457P) is associated with sub-optimal NE transport in a subject without OI.

Applicants further argue that the disclosure is sufficient to enable one skilled in the art to carry out the invention commensurate with scope of the claims, because the specification discloses sequences ESQ ID No.1 and 2 of NET, which can used to identify polymorphisms in any exon of the NET. Applicants also point out to a specific example using Chinese hamster ovary transfection to test the specific polymorphism (A457P) and argue that it can be adapted to screen any polymorphism in NET gene. Applicants' arguments are fully considered and found not persuasive because only some mutations in NET gene would result in altering an amino acid and result an abnormal polypeptide. The specification does not enable that all polymorphisms of NET gene would result in an aberrant polypeptide and result in a sub-optimal NE transport.

Applicants also argue that the various pharmacological tests disclosed in the specification can be used as further evidence of in vivo sub-optimal NET function and argues that the

specification as filed teaches techniques that can be used to identify polymorphisms in NET polypeptides present in subjects and to identify polymorphisms that cause the sub-optimal NE transport. Applicants' arguments are fully considered and found not persuasive because these pharmacological tests are useful in screening different pharmacological compounds and their effect on sub-optimal NE transport function but not with regard to a polymorphism in NET gene and its association with the sub-optimal NE transport, in general. Further, the techniques disclosed in the specification enables a screening method for susceptibility to sub-optimal NE transport in subjects with OI but not for subjects without OI. Thus the rejection is maintained herein.

7. With regard to the rejections made in the previous office action under 35 USC 103(a), (Jacob in view of Jonsson, and Stober in view of Jacob), Applicants' arguments are fully considered and the rejections are withdrawn in view of the arguments.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782 . The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
September 15, 2004

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
9/20/04